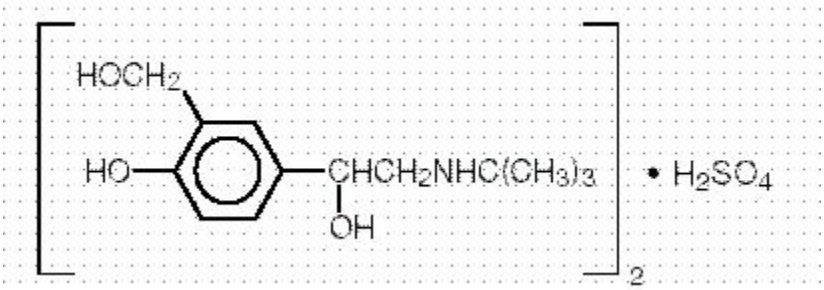
ALBUTEROL SULFATE - albuterol sulfate inhalant
Actavis Mid Atlantic LLC

DESCRIPTION

Albuterol Sulfate Inhalation Solution 0.083% contains albuterol sulfate, USP, the racemic form of albuterol, a relatively selective beta$_2$-adrenergic bronchodilator (see CLINICAL PHARMACOLOGY section below). Albuterol sulfate has the chemical name α^1-[(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene- α, α'-diol sulfate (2:1) (salt), and the following structural formula:



Albuterol sulfate has a molecular weight of 576.70 and the molecular formula $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$. Albuterol sulfate is a white crystalline powder, soluble in water and slightly soluble in ethanol.
The World Health Organization recommended name for albuterol base is salbutamol.
Each mL of Albuterol Sulfate Inhalation Solution 0.083% contains 0.83 mg of albuterol (as 1.0 mg of albuterol sulfate) in a sterile, isotonic, aqueous solution containing sodium chloride with sulfuric acid used to adjust pH between 3 and 5. The 0.083% solution requires no dilution prior to administration. Albuterol sulfate inhalation solution 0.083% contains no sulfiting agents. It is supplied in 3 mL vials for unit-dose dispensing. This product contains no preservatives.
Albuterol Sulfate Inhalation Solution 0.083% is a clear, colorless to pale yellow solution.

CLINICAL PHARMACOLOGY

The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP). The cyclic AMP thus formed mediates the cellular responses. *In vitro* studies and *in vivo* pharmacologic studies have demonstrated that albuterol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle, recent data indicate that 10 to 50% of the beta receptors in the human heart may be beta$_2$ receptors. The precise function of these receptors, however, is not yet established. Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or ECG changes.
Albuterol is longer acting than isoproterenol in most patients by any route of administration because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-*O*-methyl transferase.
Studies in asthmatic patients have shown that less than 20% of a single albuterol dose was absorbed following either IPPB or nebulizer administration; the remaining amount was recovered from the nebulizer and apparatus and expired air. Most of the absorbed dose was recovered in the urine 24 hours after drug administration. There was a significant dose-related response in FEV_1 and peak flow rate (PFR). It has been demonstrated that following oral administration of 4 mg albuterol, the elimination half-life was 5 to 6 hours.
Animal studies show that albuterol does not pass the blood-brain barrier. Recent studies in laboratory animals (minipigs, rodents, and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.
In controlled clinical trials, most patients exhibited an onset of improvement in pulmonary function within 5 minutes as determined by FEV_1. FEV_1 measurements also showed that the maximum average improvement in pulmonary function usually occurred at approximately 1 hour following inhalation of 2.5 mg of albuterol by compressor-nebulizer, and remained close to peak for 2 hours. Clinically significant improvement in pulmonary function (defined as maintenance of a 15% or more increase in FEV_1 over baseline values) continued for 3 to 4 hours in most patients and in some patients continued up to 6 hours.
In repetitive dose studies, continued effectiveness was demonstrated throughout the 3-month period of treatment in some patients.

INDICATIONS AND USAGE

Albuterol Sulfate Inhalation Solution 0.083% is indicated for the relief of bronchospasm in patients with reversible obstructive airway disease and acute attacks of bronchospasm.

CONTRAINDICATIONS
Albuterol sulfate inhalation solution is contraindicated in patients with a history of hypersensitivity to any of its components.

WARNINGS
As with other inhaled beta-adrenergic agonists, albuterol sulfate inhalation solution can produce paradoxical bronchospasm, which can be life threatening. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.
Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs and with the home use of sympathomimetic nebulizers. It is, therefore, essential that the physician instruct the patient in the need for further evaluation if his/her asthma becomes worse. In individual patients, any $beta_2$-adrenergic agonist, including albuterol inhalation solution and solution for inhalation, may have a clinically significant cardiac effect.
Immediate hypersensitivity reactions may occur after administration of albuterol as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema.

PRECAUTIONS

General
Albuterol, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias and hypertension, in patients with convulsive disorders, hyperthyroidism or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines.
Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Additionally, beta-agonists, including albuterol, when given intravenously may cause a decrease in serum potassium, possibly through intracellular shunting. The decrease is usually transient, not requiring supplementation. The relevance of these observations to the use of albuterol sulfate inhalation solution is unknown.

Information for Patients
The action of albuterol sulfate inhalation solution may last up to 6 hours and therefore it should not be used more frequently than recommended. Do not increase the dose or frequency of medication without medical consultation. If symptoms get worse, medical consultation should be sought promptly. While taking albuterol sulfate inhalation solution, other anti-asthma medicines should not be used unless prescribed.
See illustrated **“Patient’s Instructions for Use”.**

Drug Interactions
Other sympathomimetic aerosol bronchodilators or epinephrine should not be used concomitantly with albuterol.

Albuterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of albuterol on the vascular system may be potentiated.
Beta-receptor blocking agents and albuterol inhibit the effect of each other.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Albuterol sulfate, like other agents in its class, caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium in a 2-year study in the rat, at oral doses corresponding to 10, 50, and 250 times the maximum human nebulizer dose. In another study, this effect was blocked by the coadministration of propranolol. The relevance of these findings to humans is not known. An 18-month study in mice and a lifetime study in hamsters revealed no evidence of tumorigenicity. Studies with albuterol revealed no evidence of mutagenesis. Reproduction studies in rats revealed no evidence of impaired fertility.

Pregnancy

Teratogenic Effects
Pregnancy category C: Albuterol has been shown to be teratogenic in mice when given subcutaneously in doses corresponding to the human nebulization dose. There are no adequate and well-controlled studies in pregnant women. Albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A reproduction study in CD-1 mice with albuterol (0.025, 0.25, and 2.5 mg/kg subcutaneously, corresponding to 0.1, 1, and 12.5 times the maximum human nebulization dose, respectively) showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg. None were observed at 0.025 mg/kg. Cleft palate also occurred in 22 of 72 (30.5%) fetuses treated with 2.5 mg/kg isoproterenol (positive control). A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses at 50 mg/kg, corresponding to 250 times the maximum human nebulization dose.

Labor and Delivery
Oral albuterol has been shown to delay preterm labor in some reports. There are presently no well-controlled studies which demonstrate that it will stop preterm labor or prevent labor at term. Therefore, cautious use of albuterol sulfate inhalation solution is required in pregnant patients when given for relief of bronchospasm so as to avoid interference with uterine contractibility.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in some animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness of albuterol inhalation solution and solution for inhalation in pediatric patients below the age of 12 years have not been established.

ADVERSE REACTIONS
The results of clinical trials with albuterol sulfate inhalation solution in 135 patients showed the following side effects which were considered probably or possibly drug related:
Central Nervous System: tremors (20%), dizziness (7%), nervousness (4%), headache (3%), insomnia (1%).
Gastrointestinal:nausea (4%), dyspepsia (1%).
Ear, Nose and Throat**:**pharyngitis (<1%), nasal congestion (1%).
Cardiovascular:tachycardia (1%), hypertension (1%).
Respiratory:bronchospasm (8%), cough (4%), bronchitis (4%), wheezing (1%).
No clinically relevant laboratory abnormalities related to albuterol sulfate inhalation solution administration were determined in these studies.
In comparing the adverse reactions reported for patients treated with albuterol sulfate inhalation solution with those of patients treated with isoproterenol during clinical trials of 3 months, the following moderate to severe reactions, as judged by the investigators, were reported. This table does not include mild reactions.
Percent Incidence of Moderate To Severe Adverse Reactions

Reaction	Albuterol	Isoproterenol
	N = 65	**N = 65**
Central Nervous System		
Tremors	10.7%	13.8%
Headache	3.1%	1.5%
Insomnia	3.1%	1.5%
Cardiovascular		
Hypertension	3.1%	3.1%
Arrhythmias	0%	3.0%
*Palpitation	0%	22.0%
Respiratory		
**Bronchospasm	15.4%	18.0%
Cough	3.1%	5.0%
Bronchitis	1.5%	5.0%
Wheeze	1.5%	1.5%
Sputum Increase	1.5%	1.5%
Dyspnea	1.5%	1.5%
Gastrointestinal		
Nausea	3.1%	0%
Dyspepsia	1.5%	0%
Systemic		
Malaise	1.5%	0%

*The finding of no arrhythmias and no palpitations after albuterol administration in this clinical study should not be interpreted as indicating that these adverse effects cannot occur after the administration of inhaled albuterol.
**In most cases of bronchospasm, this term was generally used to describe exacerbations in the underlying pulmonary disease.

Rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema have been reported after the use of inhaled albuterol.

OVERDOSAGE

Manifestations of overdosage may include anginal pain, hypertension, hypokalemia, and exaggeration of the pharmacological effects listed in ADVERSE REACTIONS.

The oral LD_{50} in rats and mice was greater than 2,000 mg/kg. The inhalational LD_{50} could not be determined.

There is insufficient evidence to determine if dialysis is beneficial for overdosage of albuterol sulfate inhalation solution.

DOSAGE AND ADMINISTRATION

The usual dosage for adults and children 12 years and older is 2.5 mg of albuterol administered 3 to 4 times daily by nebulization. More frequent administration or higher doses are not recommended. To administer 2.5 mg of albuterol, administer the contents of one unit-dose vial (3 mL of 0.083% nebulizer solution) by nebulization. The flow rate is regulated to suit the particular nebulizer so that the albuterol sulfate inhalation solution will be delivered over approximately 5 to 15 minutes.

The use of albuterol sulfate inhalation solution can be continued as medically indicated to control recurring bouts of bronchospasm. During treatment, most patients gain optimum benefit from regular use of the nebulizer solution.

If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately, as this is often a sign of seriously worsening asthma which would require reassessment of therapy.

HOW SUPPLIED

Albuterol Sulfate Inhalation Solution 0.083% is a clear, colorless to pale yellow solution, and is supplied in 3 mL unit-dose vials containing 2.5 mg albuterol in cartons of 25, 30 and 60.

Store between 2°-25°C (36°-77°F).

Manufactured by
Cardinal Health
Woodstock, IL 60098
Manufactured for
Alpharma USPD Inc.
Baltimore, MD 21244
FORM NO. 0831A
Rev. 12/03
VC2391

PHARMACIST – DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

Patient's Instructions for Use

ALBUTEROL SULFATE INHALATION SOLUTION 0.083%*

(*Potency expressed as albuterol)

Note: This is a unit-dose vial. No dilution is required.

Read complete instructions carefully before using.

1. Twist open the top of one vial and squeeze the contents into the nebulizer reservoir (Figure 1).


Figure 1

2. Connect the nebulizer reservoir to the mouthpiece or face mask (Figure 2).

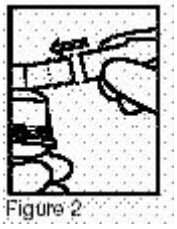


Figure 2

3. Connect the nebulizer to the compressor.

4. Sit in a comfortable, upright position; place the mouthpiece in your mouth (Figure 3) (or put on the face mask); and turn on the compressor.


Figure 3

5. Breathe as calmly, deeply, and evenly as possible until no more mist is formed in the nebulizer chamber (about 5-15 minutes). At this point, the treatment is finished.

6. Clean the nebulizer (see manufacturer's instructions).

Note: Use only as directed by your physician. More frequent administration or higher doses are not recommended.
Store between 2°-25°C (36°-77°F).
ADDITIONAL INSTRUCTIONS: _____
_____
_____
_____

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